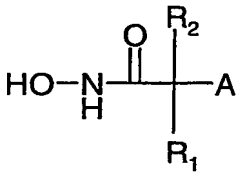
Claims

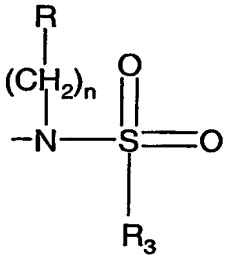
1. A method of treating cancer in a subject in need of such treatment which comprises radiotherapy, or
cytotoxic therapy in combination with heat shock,
and further comprises administering to the subject an effective amount of a matrix metalloproteinase.

2. A method of treating cancer in a subject in need of such treatment which comprises: radiotherapy,
or cytotoxic therapy in combination with heat shock,
and further comprises administering to the subject an effective amount of a matrix metalloproteinase inhibitor of the formula I



(I)

(i) wherein
A represents substituent of formula II or III;



Formula II

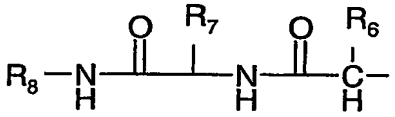
wherein

R represents hydrogen, lower alkyl, aryl-lower alkyl, aryl, mono- or poly-halo-lower alkyl, cycloalkyl, cycloalkyl-lower alkyl, (oxa or thia)-cycloalkyl, [(oxa or thia)-cycloalkyl]-lower alkyl, hydroxy-lower alkyl, acyloxy-lower alkyl, lower alkoxy-lower alkyl, lower alkyl-(thio, sulfinyl or sulfonyl)-lower alkyl, (amino, mono- or di-lower alkylamino)-lower alkyl, acylamino-lower alkyl, (N-lower alkyl-piperazino or N-aryl-lower alkylpiperazino)-lower alkyl, or (morpholino, thiomorpholino, piperidino, pyrrolidino, piperidyl or N-lower alkylpiperidyl)-lower alkyl;

R_3 represents aryl that may be unsubstituted or substituted by R_4 and R_5;

R_4 or R_5 represents independently hydrogen, lower alkyl, lower alkoxy, halogen, hydroxy, acyloxy, lower alkoxy-lower alkoxy, trifluromethyl or cyano, oxy-C2-C3-alkylene, 1- or 2-napthyl; or R_4 and R_5 together on adjacent carbon atoms represent lower alkylenedioxy;

n represents an integer from 1 to 5;



Formula III

wherein

R_6 is C_{3-12} alkyl, C_{3-12} alkenyl, C_{3-7}(optionally hydroxy-, C_{1-6} alkoxy-, amino-, or C_{1-6} alkylamino- substituted) cycloalkyl, C_{5-14} aryl, or C_{5-14} aryl(C_{1-6} alkyl), wherein aryl groups are optionally substituted by hydroxy-, C_{1-6} alkyl-, C_{1-6} alkoxy-, amino-, halo- or cyano-;

R_7 is C_{1-10} (optionally hydroxy- or C_{1-6}alkoxy- amino-, C_{1-6} alkylamino-, thiol-, C_{1-6} alkylmercapto- or protected hydroxy-, amino- or thiol- substituted) alkyl, C_{6-14} (optionally hydroxy-, C_{6-14}aryloxy-, or C_{1-6}alkoxy-, amino-, C_{1-6} alkylamino-, halo-, or cyano-substituted)aryl, or indolylmethyl;

R_8 is methyl, pyridyl, or a substituent of formula X-Y- wherein X is morpholino, pyridyl or aryl, and Y is C_{1-12}alkylene in which up to four of the methylene (-CH_2-) units are optionally replaced with -CO-, -NH-, -SO_2- or -O-;

R_1 is hydrogen, lower alkyl, aryl, aryl-lower alkyl, mono- or poly-halo-lower alkyl, cycloalkyl, cycloalkyl-lower alkyl, cycloalkyl-cycloalkyl, aryl-lower alkyl-lower cycloalkyl, lower alkyl-cycloalkyl, lower alkoxy-lower alkyl-cycloalkyl, aryl-cycloalkyl, cycloalkyl-lower alkyl-cycloalkyl, halo-lower alkyl-cycloalkyl, hydroxy-lower alkyl, acyloxy-lower alkyl, lower alkoxy-lower alkyl, aryl-lower alkoxy-lower alkyl, lower alkyl-(thio, sulfinyl or sulfonyl)-lower alkyl, (amino, mono- or di-lower alkylamino)-lower alkyl, (N-lower alkyl-piperazino or N-aryl-lower alkylpiperazino)-lower alkyl, (morpholono, thiomorpholino, piperidino, pyrrolidino, piperidyl or N-lower alkylpiperidyl)-lower alkyl, acylamino-lower alkyl, piperidyl, N-lower alkylpiperidyl or a substituent of formula IV

D-(O-(CR_9H)$_z$)$_m$-O-CH_2- Formula IV

wherein

z is 1, 2, 3 or 4;

m is 0, 1, 2 or 3;

each R_9 is

independently H, C_{1-10} (optionally hydroxy-, C_{1-6} alkoxy-, amino-, C_{1-6} alkylamino-, thiol-, C_{1-6} alkylmercapto- or protected hydroxy, amino or thiol substituted) alkyl, C_{2-6} alkenyl, C_{6-14}(optionally hydroxy-, C_{1-6} alkoxy-, amino-, C_{1-6} alkylamino-, halo- or cyano-substituted) aryl, or C_{6-14} (aryl) C_{1-6}alkyl;

D is hydrogen, C_{1-10} alkyl, C_{6-14} aryl, C_{6-14} aryl(C_{1-6} alkyl), (C_{6-14} aryl)carbonyl, or (C_{1-10} alkyl)carbonyl;

R_2 is hydrogen or lower alkyl,

(ii) or wherein

R (of formula II under (a)) and R_1 together with the chain to which they are attached from a 1,2,3,4-tetrahydro-isoquinoline, piperidine, oxazolidine, thiazolidine or pyrrolidine ring, each unsubstituted or substituted by lower alkyl; and

R_3 and R_2 have meaning as defined under (i);

(iii) or wherein

R_1 and R_2 together with the carbon atom to which they are attached form a ring system selected from lowercycloalkane which is unsubstituted or substituted by lower alkyl' oxa-cyclohexane, thia-cyclohexane, indane, tetralin, piperidine or piperidine substituted on nitrogen by acyl, lower alkyl, aryl-lower alkyl, (carboxy, esterified or amidated carboxy)-lower alkyl or by lower alkylsulfonyl; and

R_3 and R meaning as defined under (i);

or a pharmaceutically acceptable prodrug derivative thereof; or a pharmaceutically acceptable salt thereof.

3. Use of a matrix metalloproteinase inhibitor (or pharmaceutically acceptable salt or prodrug ester thereof) for the preparation of a medicament, for use in combination with
a) radiotherapy, or
b) heat shock and cytotoxic therapy for the treatment of tumors.

4. Use of a matrix metalloproteinase inhibitor (or pharmaceutically acceptable salt or prodrug ester thereof) in combination with
a) radiotherapy, or
b) heat shock and cytotoxic therapy for the treatment of tumors.

5. A package comprising a matrix metalloproteinase inhibitor (or pharmaceutically acceptable salt or prodrug ester thereof) together with instructions for use in combination with
a) radiotherapy, or
b) heat shock and cytotoxic therapy in the treatment of tumor.

6. A method according to claim 1, in which the matrix metalloproteinase inhibitor is a compound on formula I as defined in claim 2, or a pharmaceutically acceptable prodrug derivative thereof, or a pharmaceutically acceptable salt thereof.

7. A method according to claim 1, in which the matrix metalloproteinase inhibitor is one of the compounds disclosed in published international patent applications Nos. WO 98/14424, WO 97/22587 and EP 606046, or a pharmaceutically acceptable prodrug derivative thereof, or a pharmaceutically acceptable salt thereof.

8. A method according to claim 1, in which the matrix metalloproteinase inhibitor is N-hydroxy-2(R)-[[4-methoxyphenylsulfonyl](3-picolyl) amino] -3-methyl –butaneamide hydrochloride) monohydrate, or a pharmaceutically acceptable prodrug derivative thereof, or a pharmaceutically acceptable salt thereof.

9. A method according to claim 1 in which the matrix metalloproteinase inhibitor, or a pharmacologically acceptable salt or prodrug ester, is in the form of a enteral composition.

10. A method of treating cancer in a subject in need of such treatment which comprises radiotherapy in combination with heat shock therapy,
and further comprises administering to the subject an effective amount of a matrix metalloproteinase.